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EXAMINER	
O DELL, DAVID K	

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1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,293	ZHOU ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,6,15-17,25-29 and 32-40* is/are pending in the application.

4a) Of the above claim(s) *33-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,6,15-17,25-29,32,37 and 40* is/are rejected.

7)☒ Claim(s) *4, 6, 15-17, 25-29, 32, 38 and 39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/8/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This application is a 371 of PCT/US03/33980 filed 10/24/2003 which claims benefit of 60/422,355 filed 10/30/2002.

Claims 4, 6, 15-17, 25-29, 32, 33-40 are pending. Claims 33-36 are withdrawn from consideration.

Claim Rejections/Objections Withdrawn

3. The objection to the table is withdrawn, based on the examiner's misunderstanding of the table. The rejections of claims 19 & 31 under 112 2nd paragraph are withdrawn since these claims have been canceled.

Claim Rejections/Objections Maintained/ New Grounds of Rejection

4. An objection to the specification for a misspelling is maintained. A new objection to claims 4, 6, 15-17, 25-29, & 32 is raised since they now depend from a later numbered claim.

The examiner has rejected the newly amended claims 4, 6, 15-17, 25-29, 32, 37, & 40 under 112 1st paragraph for new matter. Support for the amendment to the genus of claim 37, where new values of R5 and R6 are recited cannot be found in the specification. In particular the underlined portion below:

R^5 and R^6 are each independently selected from the group consisting of:

(a) hydrogen,
(b) hydroxy,
(c) $-CH_3$,
(d) $-O-CH_3$, and
(e) oxo; or alternatively

R^5 is optionally selected from phenyl, 2-methylphenyl, -OH, benzyl, -NHBoc, and $-CO_2CH_3$; and R^6 is H;

The statements in the response state that claim 30 supports these definitions, however claims 30 does not list these groups:

30. The compound of Claim 1 wherein R^5 and R^6 are independently selected from:

(a) hydrogen,
(b) hydroxy,
(c) -CH_3,
(d) -O-CH_3, and
(e) oxo.

There is also a statement of species supporting this genus, however these species support the genus of Formula I found in claim 39, not the broad genus of claim 1 (or new claim 37).

The rejection of the newly presented and amended claims 4, 6, 15-17, 25-29, 32, 33-37, & 40 under 112 1st paragraph for scope of enablement is maintained. The applicant's representative has argued that the claims are enabled by making reference to two commonly assigned copending applications. The document US 2006-0116421 (Butora I) discloses 233 compounds of these only 6 compounds lack the CF_3 methyl group (Examples 22-24, 27, 55 & 61). Butora I has the following statements with regard to the activity:

> [0090] In particular, the compounds of the following examples had activity in binding to the CCR-2 receptor in the aforementioned assays, generally with an IC_{50} of less than about 1 μM. Such a result is indicative of the intrinsic activity of the compounds in use as modulators of chemokine receptor activity.

Since the compounds of Butora I, generally contain a trifluromethyl group (97.5% of the compounds), the general statements at [0090] are referring to these compounds. However not

withstanding these considerations, the definition of R^2 with respect to the phenyl substituents underlined below, there is nothing in the instant specification or Butora I to suggest the use of these:

R^2 is -CH_2-phenyl,

wherein phenyl is unsubstituted or substituted with 1-3 substituents independently selected from:

(a) halo,

(b) trifluoromethyl,
(c) trifluoromethoxy,
(d) hydroxy,
(e) C_{1-3}alkyl,
(f) -O-C_{1-3}alkyl,
(g) -CO_2-C_{1-3}alkyl,
(h) -CO_2H,
(i) -S-C_{1-3}alkyl,
(j) -SO_2-C_{1-3}alkyl,
(k) -SCF_3,
(l) -NH_2,
(m) -NH-SO_2-C_{1-3}alkyl, and
(n) -SO_2-NH_2;

Of course the specification teaches CF_3 as alternative substituents, but even when considering these groups in the context of Butora I, it is unreasonable to believe all these groups are active compounds. After carefully reviewing Butora I, it is clear that only hydroxy, halogen, CN, OCH_2CF_3, triazole and tetrazole were used in addition to trifluoromethyl. One could argue that tetrazole is an equivalent of the carboxylic acid group claimed (i.e. (h)) but beyond this could one argue that al these groups are obvious variants? Why would one substitute a trifluoromethyl with a sulfonamide? The same can be said for US 2005-0261325 (Butora II), which of 163 compounds teaches only 16 compounds without a trifluoromethyl group (while the applicant's

representative has pointed to 18 compounds, of these compounds 18-7, and 35 do not contain a CF_3 group). The examiner welcomes the submission of data for Examples 22-24, 27, 55 & 61 of Butora I and the examples of Butora II, which may weigh in favor of the enablement of other groups.

The examiner points again to Yang et. al. who state, "The bis-trifluoromethylbenzyl group is extremely sensitive to modification (Table 2). Both of the CF3 groups are critical for activity. Attempts to replace the bis-trifluoromethylbenzyl group with other substituted benzyl groups resulted in inactive compounds (24–27)"

Given the diverse behavior and complete lack of activity for certain groups, such prophetic recitations as those of the instant claims should be evaluated carefully. Based upon the sheer unpredictability in the art it is readily apparent that one could not make/use this very broad invention without undue experimentation. The specification gives literally no guidance with regard to what the requirements for activity are i.e. which substituents would be preferred. Medicinal chemistry is an experimental science. See *Ex parte Herzog, Hershberg, and Coan*, 115 USPQ 195 (Bd. Pat. App. & Int. 1956) affirming the examiner, and stating "it becomes obvious that the expressions defining the organic acids used.....are inclusive of inoperative materials and go far beyond the adequately disclosed subject matter of the specification." And also *Ex parte DIAMOND,* 123 USPQ 167 (Bd. Pat. App. & Int. 1959) where the examiner was affirmed for a scope of enablement rejection, and the court stated:

"the specification contains 23 specific examples, but it will be noted that they are to the preparation of relatively simple compounds.....This must be regarded as a relatively meagre and nonrepresentative disclosure to support claims which embrace millions of compounds. It should also be observed that appellant is working in a field where little prediction is possible and this Board has on several occasions held that the scope of claims should not be unduly extensive in fields where applicability is highly speculative or not explored and that subject matter which

relies upon prediction for its support is unpatentable. Ex parte Middleton, 87 USPQ 57 ; Ex parte Kauck et al., 95 USPQ 197 , Ex parte Rosenkranz et al., Pat. No. 2,715,637. In Minnesota Mining and Mfg. Co. et al. v. Carborundum Co. et al., 155 F.2d 746, 69 USPQ 288 , the court held that 'An inventor cannot disclose a small number of components which will serve as a springboard for claiming an entire class.'"

See also: *Schering Corporation v. Gilbert et al.*, 68 USPQ 84 (2d Cir. 1946)

"Theoretically a multitude of substances not as yet found in nature and not as yet compounded could be synthesized, if skilled organic chemists were given the time and materials with which to work, and actually the formulas for them could be written. There is, however, a practical limit upon synthesis, though the extent of that is not fully known, for some of the new theoretical compounds might be impossible to create, and some would be so unstable that they would disintegrate either at once or in short periods of varying length. Moreover, while analogy is at times useful, organic chemistry is essentially an experimental science and results are often uncertain, unpredictable and unexpected."

And *Nationwide Chemical Corporation, et al. v. Wright, et al.,* 192 USPQ 95 (M.D. Fla. 1976)

"with respect to generic claims to chemical and biological inventions, the scope of the claims is limited to what those skilled in the art could reasonably predict from the inventor's disclosure. This precept recognizes that one skilled in these chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances. Thus, in so-called "chemical" patent law practice, the claims of a patent are limited by the scope of what the disclosure reasonably teaches to one skilled in the art."

In re Prutton, 96 USPQ 147 (C.C.P.A. 1952)

"The complete list of organic compositions includes, in generic form, most of the organic compounds found discussed in ordinary textbooks of organic chemistry..... It appears to be appellant's view that a selection of an unsaturated hydrocarbon from the first list and of a sulphide of phosphorus from the second list will provide support for the claims here under discussion. The Examiner holds, and properly we think, that the presentation of such lists from which reagents may be selected is not a sufficient disclosure to support claims to a particular class of reaction product which might be produced by proper selection of reagents and determining the conditions of reaction."

In re Walker, 22 USPQ (C.C.P.A. 1934)

"It is true, as argued by counsel, that appellant is entitled to claim not only the substance enumerated by him in his specification, but also their equivalents. However, in cases of this character, involving chemicals and chemical compounds, many of which of course differ radically in their properties, it must appear in the specification, either by the enumeration of a

sufficient number of the members of a group or by other appropriate language, that "the chemicals or chemical combinations included therein were generally capable of accomplishing the desired result." See *In re Ellis*, 37 App. D. C. 203; *In re Dosselman*, 37 App. D. C. 211; *In re Langmuir*, 20 C. C. P. A. (Patents) 733, 62 F. (2d) 93."

In Re Sus and Schaefer 134 USPQ 1962 301-310 (*affirmed*):

"It is, however, consistent with this public purpose embodied in the pertinent statutory requirement that the *invention claimed* shall be no broader than the *invention set forth* in the written description forming a part of the specification……thus it seems to us that one killed in this art would not be taught by written description of the invention in the specification that any 'aryl or substituted aryl radical' would be suitable for the purposes of the invention but rather that only *certain aryl radicals* and certain specifically substituted aryl radicals would be suitable for such purposes." Emphasis in Original.

The examiner has made his case for the enablement rejection and the rejection may be obviated by narrowing the claims and or providing supporting evidence.

This application contains claims drawn to a nonelected invention. A complete reply to this action must include a cancellation of nonelected claims or other appropriate action.

Under examination, is group IV :

Group IV, drawn to compounds and compositions reading on claim 3, Formula Ib or If, m is 1 or 2, n is 1, Z is O or CH, X is –(C=O)NH-, R2 is benzyl, drawn to piperidinyl-pyrollidinyl-benzamides, shown as structure IV in Figure 1, compounds and compositions reading on claim 3, Formula Ib or If, m is 1 or 2, n is 1, Z is NH, X is –(C=O)NH-, R2 is benzyl, drawn to piperazinyl-pyrollidinyl-benzamides, shown as structure IX in Figure 1, compounds and compositions reading on claim 3, Formula Ib or If, m is 1 or 2, n is 0, Z is C, X is –(C=O)NH-, R2 is benzyl, drawn to bis-pyrollidinyl-benzamides, shown as structure X in Figure 1, and compounds and compositions reading on claim 3, Formula Ib or If, m is 1 or 2, n is 2, Z is C, X is –(C=O)NH-, R2 is benzyl, drawn to azepinyl-pyrollidinyl-benzamides, shown as structure XII in Figure 1.

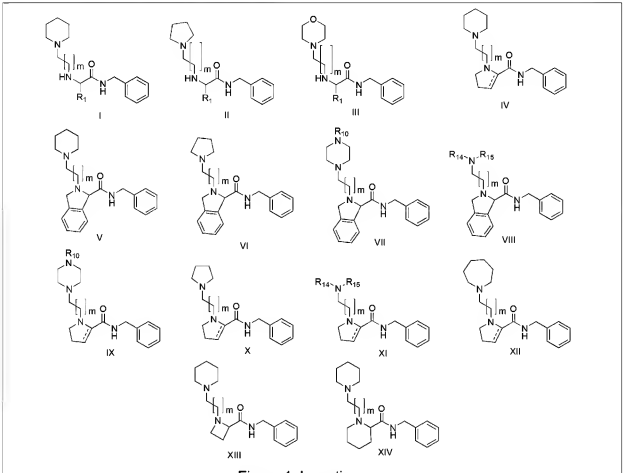


Figure 1. Inventions

Objections

Claims 4, 6, 15-17, 25-29, & 32 are objected to for depending from a higher numbered claim.

A series of singular dependent claims is permissible in which a dependent claim refers to a preceding claim which, in turn, refers to another preceding claim.

A claim which depends from a dependent claim should not be separated by any claim which does not also depend from said dependent claim. It should be kept in mind that a dependent claim may refer to any preceding independent claim. In general, applicant's sequence will not be changed. See MPEP § 608.01(n).

Claims 38 and 39 are objected to for depending from a rejected base claim would otherwise be allowable.

Specification

The spelling of "dedydroproline", on page 51 and other pages is probably meant to be dehydroproline

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 4, 6, 15-17, 25-29, 32, 37, & 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. Support for the amendment to the genus of claim 37, where new values of R5 and R6 are recited cannot be found in the specification. In particular the underlined portion below:

R^5 and R^6 are each independently selected from the group consisting of:

(a) hydrogen,
(b) hydroxy,
(c) $-CH_3$,
(d) $-O-CH_3$, and
(e) oxo; or alternatively

R^5 is optionally selected from phenyl, 2-methylphenyl, -OH, benzyl, -NHBoc, and -CO_2CH_3; and
R^6 is H;

4. Claims 1, 3, 4, 6, 10-18, 22-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds it does not reasonably provide enablement for the scope of compounds bearing the extensive list of substituents. The compounds that are enabled are as follows: In Formula Id R_2, R_3, R_4, R_{11} or R_{12} (the only variables remaining after restriction), R_2 should be limited to benzyl with a very small list of groups.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing all heterocycles, carbocycles and other groups bearing multiple substitutions of unascertainable

structure. **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds and such compounds should have activity at CCR2 receptor. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic/medicinal chemist. **(C) The state of the prior art: (E) The level of predictability in the art: (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** Each one of the factors (**C, E-H**) will be discussed in light of the scientific literature when such a factor is being directly pointed to a large capital letter referring to the aforementioned Wands factor will be placed directly after such a remark or explication. The examiner will first consider the Markush structures Ib and If.

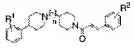
While chemical limitations are important more significantly and more importantly are the limitations of activity at CCR2. What are the important structural features for the claimed utility? It is clear from the data in the specification that the structural features of the compound are of paramount importance for activity. The only information we are given as to what the molecular determinants are for activity at CCR2 receptor is reproduced here:

> In particular, the compounds of the following examples had activity in binding to the CCR-2 receptor in the aforementioned assays, generally with an IC_{50} of less than about 1 μM. Such a result is indicative of the intrinsic activity of the compounds in use as modulators of chemokine receptor activity.

While the paucity of compounds in the specification (only 22), and no data make a complete evaluation difficult, all the compounds have two trifluoromethyl group on the benzyl group and very small groups elsewhere (mostly H). **(H)** The medicinal chemistry of CCR2 is relatively well-developed and many limitations are well known in the art. It is sensitive to structural changes that may be relatively minor in the chemical sense see Xia et. al. "Synthesis and biological evaluation of phenyl piperidine derivatives as CCR2 antagonists" *Bioorganic &*

Medicinal Chemistry Letters **2007**, *17*, 5964-5968, whole document. In particular compound **3m** is essentially inactive at 25uM and differs from potent antagonists only by the identity and position of a halogen atom.

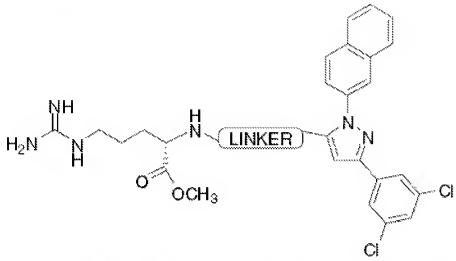
Table 2. Analogs containing a second piperidine ring of structure 3 from Figure 1

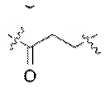
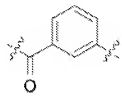
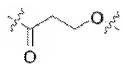


Compound	R^1	n	R^2	CCR2B binding IC_{50} (μM)
3a	2-Methoxy	1	3,4-Dichloro	11.1
3b	3-Methoxy	1	3,4-Dichloro	4.6
3c	4-Methoxy	1	3,4-Dichloro	0.32
3d	4-Dimethylamino	1	3,4-Dichloro	0.95
3e	4-Hydroxy	1	3,4-Dichloro	0.51
3f	4-Methyl	1	3,4-Dichloro	2.2
3g	4-Chloro	1	3,4-Dichloro	0.30
3h	4-Chloro	1	3,4-Difluoro	2.6
3j	4-Chloro	1	3,4-Dimethoxy	5.9
3k	4-Chloro	1	3-Trifluoromethyl	1.4
3l	4-Chloro	1	4-Bromo	5.2
3m	4-Chloro	1	2-Fluoro-4-bromo	17% at 25 μM
3u	4-Chloro	2	3,4-Dichloro	2.9

In Anthony B. Pinkerton "Diaryl substituted pyrazoles as potent CCR2 receptor antagonists" *Bioorganic & Medicinal Chemistry Letters* **2007**, *17*, 807–813, a study of structure activity relationships reveals the unpredictable and sensitive nature of CCR2 ligands to the structure of the compound:

Table 2. Linker modifications



Compound	LINKER	CCR2 IC_{50} (nM)[a]	Chemotaxis IC_{50} (nM)
30		4741	NT[c]
31		NA[b]	NT[c]
32		NA[b]	NT[c]
33		62	118

[b] NA denotes not active <10 μM concentration.

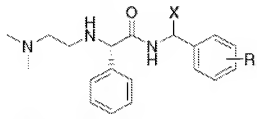
Replacement of an ethyl group in **30** for a phenyl in **32** gave inactive compounds. Where the author stated, "It appears that the SAR is relatively tight for modifications in this area. For example, shortening the chain one carbon, as in **30**, leads to a precipitous drop in activity to 4741 nM. Analog **31** highlights the importance of the central amide for potency—removal of the carbonyl gives a compound that is inactive. Likewise, constraining the linker as in phenyl analog **32** gives an inactive compound."

Perhaps more tellingly are compounds developed by Yang et. al. which are remarkably similar to those of the instant case, Yang et. al. "Discovery of 3,5-bis(trifluoromethyl)benzyl L-arylglycinamide based potent CCR2 antagonists" *Bioorganic & Medicinal Chemistry Letters* **2006**, *16*, 3735–3739. An SAR of the benzylic amide moiety, revealed severe restraints upon the identity of the substituents,

"The **bis-trifluoromethylbenzyl group is extremely sensitive to modification (Table 2). Both of the CF3 groups are critical for activity. Attempts to replace the bis-trifluoromethylbenzyl group with other substituted benzyl groups resulted in inactive compounds (24–27)** as shown in Table 2. The introduction of a methyl at the benzylic position is a way of restricting the number of low-energy conformations at this region, potentially favoring a more active conformation. Unfortunately, in this instance it greatly reduced the binding of compound 28 as compared with the parent 13."

Table 2 is reproduced below for convenience:

Table 2. Binding affinity to human CCR2 (CHO).



Compound	X	R	Binding IC_{50} (nM)
24	H	2-CF_3	1%
25	H	3-CF_3	5%
26	H	4-CF_3	7%
27	H	3,5-DiMe	0%
28	Me	3,5-$DiCF_3$	28%
13	H	3,5-$DiCF_3$	1000

% inhibition at 1 μM when no IC_{50}'s were measured.

We have been given no information in regard to the molecular determinants of receptor affinity for the compounds of the instant case, however at least for the bis-CF3 benzyl group the identity cannot be changed and maintain activity. **(F & G)** In this case these compounds bear a remarkable structural resemblance to one another, yet the claims are not commensurate in scope. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention

that has only 22 examples (that may or may not have activity at CCR2) in this unpredictable art without undue experimentation. **(C, E, F, G, H).**

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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